Claim 37 is directed to a method of inhibiting bone resorption using a modulator of OPGbp wherein the modulator is an antibody or fragment thereof which binds OPGbp. Support for the claimed invention is found at p. 18, lines 4-10 of the specification. Claim 38 is directed to an antibody or fragment thereof of Claim 37 which is an antagonist antibody. Support for the claimed invention is found at p. 22, lines 20-25 of the specification. The dependency of Claims 39, 40, 42, 44 and 47 has been amended and Claims 48 and 49 have been amended for clarity.

Claim 49 is objected to under 37 CFR 1.75 (c) as being in improper form because a multiple dependent claim shall not serve as a basis for any other multiple dependent claim. Claim 49 has been amended and is believed to be in proper form.

Rejection under 35 U.S.C. 112

Claims 37-49 are rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly does not enable one to make and/or use the invention. The Examiner argues that undue experimentation would be required to practice the invention, citing the criteria for undue experimentation set forth in *In re Wands* 8 USPQ2d 1400 (Fed, Cir. 1988). The Examiner sets forth the following arguments:

Claim 37 is directed to modulators of OPGbp. The Examiner, citing the specification at p. 22, lines 10-29, argues that modulators include antisense nucleic acids specific to OPGbp mRNA. The Examiner argues the unpredictability in the art of antisense therapy as evidenced by a number of factors which need to considered in developing an antisense therapeutic.

Claims 38-47 are directed to antibodies and compositions thereof which are modulators of OPGbp. The Examiner alleges that "the properties of OPG and OPGbp are unknown" and further argues that one could not predict what affect an antibody binding to an OPGbp epitope would have, whether it would be as an agonist, antagonist, or have no affect on OPGbp activity. In view of this, the Examiner concludes that it would require inventive experimentation to determine the effects of antibody binding to a given epitope.

Claim 48 is directed to a method of treating bone disease comprising administering an OPGbp modulator in combination with other factors for protecting bone. The Examiner argues that bone homeostasis is regulated by the actions of osteoblasts and osteoclasts and mentions that some factors recited in the claim regulate osteoclast formation while other factors regulate osteoblast formation. In rejecting this claim, the Examiner appears to argue the unpredictability of administering an OPGbp

modulator in combination with another bone protecting agent for treating a bone disease, citing as an example the combination of IL-1 and an OPGbp antibody, and further alleges that the action of a combined administration is dependent upon the disease being treated.

Claim 49 is directed to a method of treating various bone diseases. The Examiner argues that the "treatment of any disease relies to some extent in counteracting the causative agent" and mentions that osteomyelitis, one the diseases specified in the claims, is caused by pathogenic bacteria while another disease, Paget's disease, does not have a known cause but may result from genetic mutation or viral infection. It is alleged that because "causative agents" could be different in the different recited diseases, it would be unpredictable whether an OPGbp modulator would be effective in treating the diseases recited in the claim and therefore undue experimentation would be required.

In addition to the lack of predictability in the art, the Examiner alludes to extensive experimentation, a lack of direction in the specification, and a lack of examples of OPGbp anti-sense therapy or antibody therapy in vivo as evidence that undue experimentation would be required to carry out the claimed invention. The Examiner concludes with the allegation that "there is no known evidence to support the benefit or treatment of a bone disease with a modulator or antibody to OPGbp."

Applicant maintains that the Examiner has not met the burden of establishing nonenablement of the pending claims. The arguments presented focus almost exclusively on the unpredictability in the art and are largely speculative and without substantiation. For example, the Examiner completely disregards the teachings of the present application and simply states as fact that the properties of OPG and OPGbp are "unknown". The Examiner has relied on this unsubstantiated "fact" to argue that undue experimentation would be required to identify agonist or antagonist antibodies. As a second example, the Examiner does not offer any evidence relating to the alleged unpredictability of using a combination of an OPG modulator and one of the claimed bone protection factors to treat a bone disease, other than to merely speculate that different factors may affect bone loss by different mechanisms. Yet no evidence has been presented to indicate that this would result in undue experimentation. Finally, the allegation that "causative agents" are different for different bone diseases, even assuming that it is true, does not by itself lead to a conclusion of unpredictability and lack of enablement. However, even assuming for the sake of argument that a case for nonenablement has been made, Applicant hereby sets forth evidence sufficient to rebut the position.

The Examiner's allegation that the properties of OPG and OPGbp are "unknown" is clearly contradicted by the teachings in the present application, in particular Examples 8 and 9. The application teaches that OPGbp stimulates osteoclast formation in vitro and stimulates hypercalcemia and bone resorption in vivo. The application also teaches that by blocking OPGbp activity (by addition of OPG) osteoclast formation in vitro is decreased and hypercalcemia associated with increased bone resorption in vivo is also decreased. Contrary to the Examiner's position, the biological function of OPGbp has been characterized and disclosed in the present application and the effects of blocking OPGbp activity have also been documented.

It would be apparent to one skilled in the art that, given the teachings of the specification, modulators of OPGbp activity which are either agonists or antagonists are readily identified by assays such as those described in Examples 8 and 9 of the specification. In particular, the assays described in Example 9 provide in vivo biological data as well. The level of skill in the art is such that these assays may be readily carried out.

The application teaches modulators of OPGbp and in particular teaches OPGbp antibodies. Specific procedures for generating antibodies which bind OPGbp are set forth in the specification in Example 11 starting at p. 46 of the specification. In addition, techniques known to one skilled in the art were available for the production of chimeric, CDR-grafted, humanized and fully human antibodies which bind OPGbp. As indicated above, the specification provides in Examples 8 and 9 in vitro and in vivo assays for determining the effects of OPGbp antibodies on OPGbp activity.

Whether the effects of a modulator of OPGbp activity can be predicted is only one criteria for enablement. It has been pointed out that the specification teaches one skilled in the art how to obtain a modulator of OPGbp and to evaluate the properties of said modulator on in vitro and in vivo OPGbp activity. In particular, the specification teaches the production of antibodies which bind OPGbp and identify either antibody agonists and antagonists of OPGbp activity. Undue experimentation would clearly not be required to identify such antibodies.

The bone protecting factors recited in Claim 48 were known in the art to either inhibit bone resorption by decreasing the number and/or activity of osteoclasts, or promote bone growth primarily by increasing the number and/or activity of osteoblasts. With this knowledge, one skilled in the art could readily test the various combinations in Claim 48 in an in vitro and in vivo assay such as those described in Examples 8 and 9 of the specification to determine the combined effects on osteoclast formation and bone

resorption. For those combinations involving factors which affect osteoblast activity, in vivo assays known in the art which measure bone resorption could be used. As indicated below, the results from assays such as those in Example 8 and 9 are predictive for the use of the claimed combinations in treating bone disease.

The bone diseases set forth in Claim 49 are characterized by an increase in bone resorption. It was known in the art that increased bone resorption is mediated by increased numbers and activity of osteoclasts, which are the predominant cells responsible for breaking down and resorbing bone. Consequently, the ability of an OPG modulator to block osteoclast formation and bone resorption is predictive of the usefulness of such a compound in treating the claimed bone diseases. The Examiner's reliance on differences in the "causative agents" of the claimed diseases ignores the end result generated by these apparently different "causative agents" namely increased bone resorption that is mediated by osteoclasts. Modulators, such as antibodies, which block OPGbp activity will block osteoclast formation, inhibit bone resorption and treat the claimed bone diseases. The ability of a modulator to block OPGbp activity as evidenced by the in vitro and in vivo assays disclosed in the specification is predictive of the use of said modulator in treating bone diseases.

The Examiner has also alluded to the lack of working examples in the specification. Examples 8 and 9 have shown that OPG is in fact an antagonist of OPGbp activity. This teaching enables one to predict that other modulators which are antagonists of OPGbp activity will likely exist. One skilled in the art could, for example, use OPG as a model for generating other antagonists. While an antibody which is an antagonist of OPGbp activity has not been exemplified, the specification teaches one how to generate and identify such antibodies.

For these reasons, it is submitted that the originally filed Claims 37-49 are fully enabled by the specification and no undue experimentation is required to carry out the claimed invention. Applicant has requested amendments to certain claims solely for the purpose of advancing prosecution and without acquiescing to the rejection. It is also submitted that Claims 37-49 as amended are also fully enabled by the specification.

CONCLUSION

In view of the amendments and remarks set forth above, Claims 37-49 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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